Claims

1. A compound of formula (I)

$$A\text{-}B\text{-}X^1\text{-}T^1(R^2)\text{-}L^1\text{-}T^2(R^3)\text{-}X^2\text{-}Q \qquad (I)$$

wherein:

A is 5- or 6-membered monocyclic aromatic ring containing 1, 2 or 3 ring heteroatoms selected from nitrogen, oxygen and sulphur atoms optionally substituted by one, two or three atoms or groups selected from halo, oxo, carboxy, trifluoromethyl, cyano, amino, hydroxy, nitro, C_{1-4}alkyl (for example methyl or ethyl), C_{1-4}alkoxy (for example methoxy or ethoxy), C_{1-4}alkoxycarbonyl, C_{1-4}alkylamino (for example methylamino or ethylamino) or di-C_{1-4}alkylamino (for example dimethylamino or diethylamino);

B is a phenylene ring optionally substituted by one or two substituents selected from halo, trifluoromethyl, trifluoromethoxy, cyano, nitro, C_{1-4}alkyl, C_{2-4}alkenyl and C_{2-4}alkynyl, from the substituent $-(CH_2)_n Y^1$ wherein n is 0-4 and Y^1 is selected from hydroxy, amino, carboxy, C_{1-4}alkoxy, C_{2-4}alkenyloxy, C_{2-4}alkynyloxy, C_{1-4}alkylamino, di-C_{1-4}alkylamino, pyrrolidin-1-yl, piperidino, morpholino, thiomorpholino, 1-oxothiomorpholino, 1,1-dioxothiomorpholino, piperazin-1-yl, 4-C_{1-4}alkylpiperazin-1-yl, C_{1-4}alkylthio, C_{1-4}alkylsulphinyl, C_{1-4}alkylsulphonyl, C_{2-4}alkanoylamino, benzamido, C_{1-4}alkylsulphonamido and phenylsulphonamido, from the substituent $-(CH_2)_n Y^2$ wherein n is 0-4 and Y^2 is selected from carboxy, carbamoyl, C_{1-4}alkoxycarbonyl, N-C_{1-4}alkylcarbamoyl, N,N-di-C_{1-4}alkylcarbamoyl, pyrrolidin-1-ylcarbonyl, piperidinocarbonyl, morpholinocarbonyl, thiomorpholinocarbonyl, 1-oxothiomorpholinocarbonyl, 1,1-dioxothiomorpholinocarbonyl, piperazin-1-ylcarbonyl, 4-C_{1-4}alkylpiperazin-1-ylcarbonyl, C_{1-4}alkylsulphonamidocarbonyl, phenylsulphonamidocarbonyl and benzylsulphonamidocarbonyl, from a substituent of the formula $-X^3\text{-}L^2\text{-}Y^2$ wherein X^3 is a group of the formula $CON(R^5)$, $CON(L^2\text{-}Y^2)$, $C(R^5)_2O$, O, $N(R^5)$ or $N(L^2\text{-}Y^2)$, L^2 is C_{1-4}alkylene, Y^2 has any of the meanings defined immediately hereinbefore and each R^5 is independently hydrogen or C_{1-4}alkyl, and from a substituent of the formula $-X^3\text{-}L^3\text{-}Y^1$ wherein X^3 is a group of the formula $CON(R^5)$, $CON(L^3\text{-}Y^1)$, $C(R^5)_2O$,

O, N(R^5) or N(L^3-Y^1), L^3 is C_{2-4}alkylene, Y^1 has any of the meanings defined immediately hereinbefore and each R^5 is independently hydrogen or C_{1-4}alkyl, and

wherein any heterocyclic group in a substituent of B optionally bears 1 or 2 substituents selected from carboxy, carbamoyl, C_{1-4}alkyl, C_{1-4}alkoxycarbonyl, N-C_{1-4}alkylcarbamoyl and N,N-di-C_{1-4}alkylcarbamoyl, and wherein any phenyl group in a substituent of B optionally bears 1 or 2 substituents selected from halo, trifluoromethyl, cyano, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl,

C_{1-4}alkoxy, C_{2-4}alkenyloxy and C_{2-4}alkynyloxy;

T^1 is CH or N;

T^2 is CH or N;

with the proviso that at least one of T^1 and T^2 is N and wherein the heterocyclic ring formed by T^1, T^2, L^1, R^2 and R^3 is optionally substituted by one or two substituents selected from hydroxy, oxo, carboxy and C_{1-4}alkoxycarbonyl; or one of the following:

$-(CH_2)_n-R$, $-(CH_2)_n-NRR^1$, $-CO-R$, $-CO-NRR^1$, $-(CH_2)_n-CO-R$ and $-(CH_2)_n-CO-NRR^1$;

wherein n is 0, 1 or 2, preferably n is 1 or 2;

R and R^1 are independently selected from hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, hydroxyC_{1-4}alkyl, carboxyC_{1-4}alkyl and C_{1-4}alkoxycarbonylC_{1-4}alkyl or where possible R and R^1 may together form a 5- or 6-membered optionally substituted saturated or partially unsaturated (preferably saturated) heterocyclic ring which may include in addition to the nitrogen to which R and R^1 are attached 1 or 2 additional heteroatoms selected from nitrogen, oxygen and sulphur

X^1 is SO, SO_2, $C(R^4)_2$ or CO when T^1 is CH or N; or in addition X^1 is O or S when T^1 is CH;

and wherein each R^4 is independently hydrogen or C_{1-4}alkyl;

L^1 is C_{1-4} alkylene or C_{1-3}alkylenecarbonyl;

R^2 is hydrogen or C_{1-4}alkyl;

R^3 is hydrogen or C_{1-4}alkyl;

or R^2 and R^3 are joined to form a C_{1-4}alkylene or $-CH_2CO-$ group; wherein the ring formed by T^1, R^2, R^3, T^2 and L^1 is optionally substituted; with the proviso that when T^1 and T^2 are both N, L^1 is not methylene and R^2 and R^3 together are not methylene;

X^2 is S(O)$_y$ wherein y is one or two, $C(R^5)_2$ or CO; and each R^5 is hydrogen or C_{1-4}alkyl;

Q is phenyl, naphthyl, phenylC_{1-4}alkyl, phenylC_{2-4}alkenyl, phenylC_{2-4}alkynyl or a heterocyclic moiety containing up to 4 heteroatoms selected from nitrogen, oxygen and sulphur and Q is optionally substituted by one, two or three substituents selected from halo, trifluromethyl, trifluoromethoxy, cyano, hydroxy, amino, nitro, trifluoromethylsulphonyl, carboxy, carbamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{2-4}alkenyloxy, C_{2-4}alkynyloxy, C_{1-4}alkylthio, C_{1-4}alkylsulphinyl, C_{1-4}alkylsulphonyl, C_{1-4}alkylamino, di-C_{1-4}alkylamino, C_{1-4}alkoxycarbonyl, N-C_{1-4}alkylcarbamoyl, N,N-di-C_{1-4}alkylcarbamoyl, C_{2-4}alkanoyl, C_{2-4}alkanoylamino, hydroxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, carboxyC_{1-4}alkyl, C_{1-4}alkoxycarbonylC_{1-4}alkyl, carbamoylC_{1-4}alkyl, N-C_{1-4}alkylcarbamoylC_{1-4}alkyl, N,N-di-C_{1-4}alkylcarbamoylC_{1-4}alkyl, phenyl, heteroaryl, phenoxy, phenylthio, phenylsulphinyl, phenylsulphonyl, benzyl, benzoyl, heteroaryloxy, heteroarylthio, heteroarylsulphinyl and heteroarylsulphonyl, and wherein said heteroaryl substituent or the heteroaryl group in a heteroaryl-containing substituent is a 5- or 6-membered monocyclic heteroaryl ring containing up to 3 heteroatoms selected from nitrogen, oxygen and sulphur, and wherein said phenyl, heteroaryl, phenoxy, phenylthio, phenylsulphinyl, phenylsulphonyl, heteroaryloxy, heteroarylthio, heteroarylsulphinyl, heteroarylsulphonyl, benzyl or benzoyl substituent optionally bears 1, 2 or 3 substituents selected from halo, trifluoromethyl, cyano, hydroxy, amino, nitro, carboxy, carbamoyl, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylamino, di-C_{1-4}alkylamino, C_{1-4}alkoxycarbonyl, N-C_{1-4}alkylcarbamoyl, N,N-di-C_{1-4}alkylcarbamoyl and C_{2-4} alkanoylamino;

and pharmaceutically acceptable salts thereof.

2. A compound of formula (I) according to claim 1 wherein A is a pyridyl, pyrimidinyl or pyridazinyl ring.

3. A compound of formula (I) according to claim 2 wherein A is 4-pyrimidinyl or 4-pyridyl.

4. A compound of formula (I) according to any one of claims 1 to 3 wherein B is paraphenylene.

5. A compound of formula (I) according to any one of claims 1 to 4 wherein the ring formed by T^1, R^2, R^3, T^2 and L is 1,4-piperazinediyl.

6. A compound of formula (I) according to any one of claims 1 to 5 wherein X^1 is CO.

7. A compound of formula (I) according to any one of claims 1 to 6 wherein X^2 is SO_2.

8. A compound of formula (I), as defined in claim 1, wherein

A is pyridyl, pyrimidinyl, or pyridazinyl;

B is para-phenylene;

X^1 is CO, SO_2 or CH_2;

T^1 and T^2 are both N;

L^1 is ethylene or propylene;

R^2 and R^3 are joined to form an ethylene or propylene or methylenecarbonyl group;

X^2 is SO_2;

Q is styryl or naphthyl optionally substituted by fluoro, chloro or bromo or is phenyl optionally substituted by fluorophenyl, chlorophenyl, or bromophenyl;

and pharmaceutically-acceptable salts thereof.

9. A compound of formula (I) selected from:

1-(6-bromonaphth-2-ylsulphonyl)-4-[4-(4-pyrimidinyl)benzoyl]piperazine;

1-(6-chloronaphth-2-ylsulphonyl)-4-[4-(4-pyridyl)benzoyl]piperazine;

1-(6-bromonaphth-2-ylsulphonyl)-4-[4-(4-pyradazinyl)benzoyl]piperazine;

and pharmaceutically-acceptable salts thereof.

10. A compound of formula (I) according to any one of claims 1 to 9 for use in medical therapy.

11. A pharmaceutical formulation comprising a compound of formula (I) according to any one of claims 1 to 9 and a pharmaceutically-acceptable diluent or carrier.

AMENDED SHEET

12. Use of a compound of formula (I) according to any one of claims 1 to 9 in the preparation of a medicament for use in producing a Factor Xa inhibiting effect.

13. A method of preventing or treating a Factor Xa mediated disease or medical condition comprising administering to a patient a pharmaceutically effective amount of a compound of formula (I), as defined in any one of claims 1 to 9.

14. A process for preparing a compound of formula (I), are defined in claim 1, comprising:

(a) for the production of those compounds of the formula (I) wherein T^1 is N and X^1 is CO, the reaction, conveniently in the presence of a suitable base, of an amine of formula (II)

$$HN(R^2)\text{-}L^1\text{-}T^2(R^3)\text{-}X^2\text{-}Q \qquad (II)$$

with an acid of the formula (III)

$$A\text{-}B\text{-}COOH \qquad (III)$$

or a reactive derivative thereof;

(b) for the production of those compounds of the formula (I) wherein T^1 is CH and X^1 is O by the reaction, conveniently in the presence of a suitable coupling agent, of a compound of the formula (IV):

$$Z\text{-}CH(R^2)\text{-}L^1\text{-}T^2(R^3)\text{-}X^2\text{-}Q \qquad (IV)$$

wherein Z is a displaceable group, with a phenolic compound of the formula (V):

$$A\text{-}B\text{-}OH \qquad (V);$$

(c) for the production of those compounds of the formula (I) wherein T^1 is N and X^1 is $CH(R^4)$, the reductive amination of a keto compound of the formula (VI):

$$A\text{-}B\text{-}CO\text{-}R^4 \qquad (VI)$$

wherein R^4 is hydrogen or C_{1-4} alkyl, with an amine of the formula (II) as defined above;

(d) the reaction of a compound of the formula (VII):

$$Z\text{-}B\text{-}X^1\text{-}T^1(R^2)\text{-}L^1\text{-}T^2(R^3)\text{-}X^2\text{-}Q \qquad (VII)$$

wherein Z is a displaceable group with an activated derivative of ring A;

(e) by forming A ring on compounds of formula (VII), wherein Z is a functional group capable of cyclisation;

(f) for the production of compounds wherein T^2 is N, the reaction of a compound of the formula (VIII):

$$A\text{-}B\text{-}X^1\text{-}T^1(R^2)\text{-}L^1\text{-}NH(R^3) \qquad (VIII)$$

with a compound of the formula (IX):

$$Z\text{-}X^2\text{-}Q \qquad (IX)$$

wherein Z is a displaceable group;

(g) for the production of compounds wherein T^1 is N and X^1 is SO or SO_2, the reaction of a compound of the formula (II) as defined above with a compound of the formula (X):

$$A\text{-}B\text{-}SO_x\text{-}Z \qquad (X)$$

wherein x is one or two and Z is a displaceable group;

(h) for production of compounds of formula (I) by coupling T^2 to Q and thus preparing the $-T^2-X^2-Q$ moiety, methods analogous to those described in process variants (a), (c) and (g) for preparing the $B-X^1-T^1-$ moiety may be employed;

(i) for the production of compounds of formula (I) wherein X^1 is a group of the formula SO, SO_2, wherein B bears a C_{1-4}alkylsulphinyl, C_{1-4}alkylsulphonyl, 1-oxothiomorpholino or 1,1-dioxothiomorpholino group, wherein X^2 is a group of the formula SO or SO_2 wherein Q bears a C_{1-4}alkylsulphinyl, C_{1-4}alkylsulphonyl, phenylsulphinyl, phenylsulphonyl, heteroarylsulphinyl or heteroarylsulphonyl group, the oxidation of the corresponding compound of the formula (I) which contains X^1 as a thio group.